UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,493	07/18/2000	Jack Wands	MGH-0026	3498

7590 01/25/2005

Paul K Legaard
Woodcock Washburn Kurtz Mackiewicz & Norris
46th Floor
One Liberty Place
Philadelphia, PA 19103

EXAMINER	
LIETO, LOUIS D	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,493	WANDS ET AL.	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/09/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6-8,17,20-28,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6-8,17,20-28,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed on 11/09/2004 has been entered. Claims 4, 6-8, 17, 20-28, and new claims 47 and 48 are under consideration. Please note that the examiner of record has changed to Dr. Louis D. Lieto of Art Unit 1632.

Claim Rejections - 35 USC § 103

In view of Applicant's amendments to the claims the 103(a) rejection of claims 4, 6-8, 17, and 20-28 over is withdrawn.

The rejection of claims 4, 6-8, 17, 20-28, 34 and 36-38 under 35 U.S.C. 103(a) as being unpatentable over Maertens et al. (WO 96/13590, 9 May 1996) or Maertens et al. (US 2002/0183508 Al, December 5, 2002) or Selby et al. (J Gen. Virol. 74:1103-11 13, 1993) or Donnelly et al. (WO 97/47358, 18 December, 1997) in view of Liao et al. (WO 96/38474), Tokushige et al. (Hepatology 24:14-20, 1996) and Ferrari et al. (Hepatology 19:286-295) is withdrawn.

However, the claims are rejected based on the new grounds stated below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 6, 7, 8, 17, and 20-28 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 4, 6, 7, 8, 17, and 20-28, are drawn to a recombinant nucleic acid consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, operably linked to any 5'UTR, a promoter, an enhancer and a polyadenylation sequence. The claims are drawn to a genus of 5' UTR sequences that are defined solely by the fact that they are untranslated and 5'of the coding region of any gene. Applicant should note that this is a new rejection, which was illuminated by the addition of applicant's new claims 47 and 48. Claim 47 limits claim 6 to the 5' UTR of HCV. This indicates that applicant contemplates that claims 4, 6, 7, 8, 17, and 20-28 read on any 5'UTR from any gene.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The claimed genus contemplated in the specification includes all 5'UTRs that lead any gene in any organism, including prokaryotes, eukaryotes, plants and animals. A staggering number of nucleic acid molecules are encompassed by this genus.

The factors to be considered when assessing possession of the claimed invention include

disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the nucleic acid sequence is a 5'UTR. The specification does not contemplate any specific 5'UTRs other than 5'UTR of the HCV ORF. Further the specification fails to identify any structural feature or functional element, common to all 5'UTRs that enhance or even allow translation. 5' UTRs that form stable stem and loop structures block access by the ribosome to the first AUG codon {Kozak et al. (1999) Gene 234:187-208; pg. 191, col. 1, pgph 3}. The specification does not describe any common nucleic acid sequence(s) or structural element(s) required in order for a 5' UTR to function in an expression construct. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of 5' UTRs.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description'

inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for a recombinant nucleic acid consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, operably linked to any 5'UTR, a promoter, an enhancer and a polyadenylation sequence. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 4, 6, 7, 8, 17, 20-28, 47 and 48 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, wherein said nucleotide sequence is operably linked to regulatory elements, said regulatory elements comprising a promoter, enhancer, polyadenylation sequence, and at most the 9 most 3' nucleotides of the 5'UTR of a hepatitis C virus, does not reasonably provide enablement for a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, wherein said nucleotide sequence is operably linked to regulatory elements, said regulatory elements comprising a promoter, enhancer, polyadenylation sequence, and a 5' untranslated region from any gene The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Applicant should note that this is a new rejection based on applicant's amendment to the claims

to include any 5' UTR region from any gene. Further, it is noted that the previous examiner withdrew the rejection over a lack of enablement for a recombinant nucleic acid molecule consisting of sequences encoding HCV nonstructural proteins operably linked to regulatory elements and a 5' UTR of HCV. However, this rejection is reinstated over the claims because of the reasoning and newly cited references set forth below.

The specification does not provide an enabling disclosure for making or using a recombinant nucleic acid molecule consisting of a nucleotide sequence encoding hepatitis c virus NS3, NS4, and NS5 proteins, operably linked to a promoter, enhancer, polyA and the 5' UTR of the hepatitis C virus or any other gene. The specification on page 2 lines 22-29 discloses that the HCV genome comprises 5' and 3' UTRS and that the 5' UTR is 324-341 bp long. The specification also discloses the sequence for the 5' UTR of HCV on page 10 (lines 18-31 continued on page 11, lines 1-2), however the specification does not teach the sequence of a 5' UTR from any other gene. Further, the specification does not provide guidance on how to use any 5' UTR in the context of expressing the HCV nonstructural proteins and particularly when the nucleic acid containing the 5' UTR was to be used in treatment and in a pharmaceutical composition. It is noted that in a pharmaceutical composition or in a treatment method using a nucleic acid comprising a regulatory element, one would expect to get a higher gene expression due to the regulatory element. As stated below the ability of a 5'UTR to positively regulate translation is unpredictable base on sequence alone.

While it was conventional in the art to make and use a nucleic acid molecule comprising a promoter, enhancer and polyA which are operably linked to a nucleotides sequence encoding a protein, such as hepatitis C virus NS proteins in the instant case, it was not conventional and

routine in the art to use the 5' UTR of HCV or any other gene in an expression vector for regulating the expression of the nucleotide sequence encoding the protein. Specifically, Han et al PNAS 1991 reported that the 5' UTR of hepatitis C virus has a very strongly conserved 5' untranslated region that is similar to that of pestiviruses in terms of its size, blocks, of homologous nucleotide sequences, and the organization of small open reading frames (ORFs) (see the last paragraph in the left column on page 1711). However, Han et al did not teach as to whether the 5' UTR increased or decreased expression of a coding sequence under its control.

Additionally, it is noted that full length 5'UTR inhibits expression of viral genes (see first full paragraph on page 1105 right column in Selby et al J. Gen. Virol. 74 : 1103-1113, 1993) . Selby et al further observed that 5' leader does not promote efficient translation. This clearly indicates that expression from a construct comprising 5' UTR would produce lower levels of gene expression and it is not clear whether the claimed construct would produce sufficient protein to produce an immune response. It is specifically pointed out that applicants in their working examples used a construct that did not have the 5' UTR. Further, the 5'UTR of the hepatitis C virus, taught by Han et al. (pg. 1712, Figure 2), contains multiple, pre-mature Start codons, in all three reading frames, which would lead to initiation of ribosomal activity before the natural, in-frame, start codon of ORF in the recombinant nucleic acid molecule that encodes NS3, NS4 and NS5. Initiation sites in mRNAs are reached by a scanning mechanism that predicts that translation should start at the AUG codon nearest the 5' end of the mRNA {Kozak et al. (1999) Gene 234:187-208; Abstract}. Some, but not all, of the start codons in the HCV 5' UTR are followed by in-frame stop codons. The start codon in the 5'UTR that is not followed by a stop codon violates the first AUG rule, which states that translation begins at the AUG closest

to the 5'end {Lieto et al. (2003) J. Immunol. 5277-5286; pg. 5285, col. 1, pgph3}. This codon will lead to the production of an aberrant protein; that is either longer than the protein encoded by the nucleotide sequence of NS3, NS4 and NS5 alone, or a nonsense sequence due to translation of the wrong frame. The Start codons that are followed by in-frame Stop codons may lead to ribosomal re-initiation, which is inefficient and can reduce translation productivity {Lieto et al. (2003) J. Immunol. 5277-5286; pg. 5285, col. 1, pgph3}. Therefore, expression levels with the construct in the working examples cannot be compared with the expression level with the construct instantly recited. The lack of working examples describing the expression of a nucleic acid encoding the NS3, NS4, and NS5 proteins operably linked to a 5' UTR and the sequence hindrances in the 5' UTR of HCV make it impossible to predict that a construct containing this 5'UTR could express a functional in-frame protein.

Given the complete lack of guidance in the specification on how to construct and use a recombinant nucleic acid consisting of a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, operably linked to any 5'UTR, a promoter, an enhancer and a polyadenylation sequence, and the teachings in the art that including a 5'UTR with premature start codons in an expression vector makes translation productivity completely unpredictable based on sequence alone, the skilled artisan would be unable to practice the invention as claimed, except as a nucleotide sequence encoding hepatitis C virus nonstructural proteins NS3, NS4 and NS5, wherein said nucleotide sequence is operably linked to regulatory elements, said regulatory elements comprising a promoter, enhancer, polyadenylation sequence, and at most the 9 most 3' nucleotides of the 5'UTR of a hepatitis C virus, without extensive and undue experimentation.

All claims free of the prior art of record.

No claims allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER